PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P039126WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/004877	International filing date *(day/month/year)* 18.11.2004	Priority date *(day/month/year)* 19.11.2003
International Patent Classification (IPC) or national classification and IPC C07K7/06, A61K38/08, A61P37/04		
Applicant PEPHARM R&D LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.09.2005	21.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Groenendijk, M Telephone No. +31 70 340-3715

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004877

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-41	as originally filed

Claims, Numbers

1-21	received on 02.09.2005 with letter of 31.08.2005

Drawings, Sheets

1/5-5/5	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12-19 as to IA

because:

☒ the said international application, or the said claims Nos. 12-19 as to IA relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11,20,21
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:
D1:Derwent accession nr.:ABG03266
D2:WO0175067
D3:Hepato-Gastroenterology, Vol.32, 1996, 882-886

I.Novelty

Due to the restrictions made in the scope of claim 1, the present claims are considered to be novel under Art.33(2) PCT in view of D1-D3.

II.Inventive step

1)The closest prior art is considered to be D3, disclosing a low molecular weight glycoprotein fraction of porcine spleen and its use in the treatment of Hepatitis B.
2)The compounds of the present claims of the application essentially differ from said prior art therein that they essentially consist of the hexapeptide IVTNTT. Said compounds are also used as immunoregulating agents, particularly in the treatment of hepatitis B. The compound IVTNTT has been isolated from a porcine spleen extract, e.g., as mentioned in D3, and has been characterized by its structure. The advantage of a well-defined compound is that it can be optimized in its use and by synthesizing it, any possible transmission of unknown animal diseases originating from a natural animal spleen extract can be avoided (see description, page 10).
3)The problem to be solved may therefore be considered to be the provision of alternative compounds/compositions for the treatment of immune-related diseases which lacks said

disadvantages of the prior art composition of D3.
4)It is considered in general to belong to the normal routine of a skilled person, confronted with the problem posed, to identify the active principle in a natural extract having a certain activity and to elucidate its structure.
5)In this respect the applicant has emphasized that the prior art document D3 only refers to a mixture of low molecular weight glycopeptides, whereas the present peptide is unglycosylated. It is acknowledged that the prior art does not indicate or suggest that the active principle is an unglycosylated peptide: its presence is therefore considered to be unexpected and identification activities would also not be directed to an unglycosylated peptide.
Hence inventive step can be acknowledged to claims 1-21 under Art.33(3) PCT.

III.Industrial applicability
For the assessment of the present claims 12-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WHAT IS CLAIMED IS:

1. An isolated or purified peptide consisting of the Isoleucyl-valyl-threonyl-asparaginyl-threonyl-threonine peptide, optionally including up to 4 amino acids situated either at the carboxyl and/or amino terminal ends.
2. A peptide according to claim 1, wherein the peptide contains 1 or 2 additional amino acids.
3. A peptide according to claim 1, wherein the peptide consists of the Isoleucyl-valyl-threonyl-asparaginyl-threonyl-threonine peptide.
4. A peptide according to claim 1 wherein said peptide is L-Isoleucyl-L-valyl-L-threonyl-L-asparaginyl-L-threonyl-L-threonine (SEQ ID NO:1).
5. The peptide of claims 1 to 4 wherein said peptide reduces the symptoms of a viral disease.
6. The peptide of claim 5, wherein said viral disease is hepatitis B infection.
7. The peptide of any one of claims 1 to 6, wherein said peptide has immuno-stimulating properties.
8. A peptide according to any of the claims 1 to 7 wherein said peptide is in a substantially pure form.
9. A pharmaceutical composition comprising a peptide according to any one of claims 1 to 7.
10. A pharmaceutical composition according to claim 7 comprising L-Isoleucyl-L-valyl-L-threonyl-L-asparaginyl-L-threonyl-L-threonine.
11. A method of making a pharmaceutical composition comprising providing a peptide according to any one of claims 1 to 7 and mixing said peptide with a pharmaceutically acceptable carrier.
12. A method of reducing the effects of a human disease comprising administering a pharmaceutically effective dose of a peptide according to any one of claims 1 to 7.
13. The method of claim 12, wherein said human suffers from a viral disease.
14. The method of claim 13, wherein said viral disease is hepatitis B infection.
15. A method of stimulating the immune system of an individual comprising administering a pharmaceutically effective dose of a peptide according to any one of claims 1 to 7.
16. The use of a peptide according to any one of claims 1 to 7 as a pharmaceutical compound.

17. The use according to claim 16 wherein said compound is used for treating a viral disease.

18. The use according to claim 17, wherein said viral disease is hepatitis B infection.

19. The use of a peptide according to any one of claims 1 to 7 as an immune stimulant.

20. The use of a peptide according to any one of claims 1 to 7 as a nutritional supplement.

21. A molecule comprising an enhanced derivative of the Isoleucyl-valyl-threonyl-asparaginyl-threonyl-threonine peptide, said enhanced derivative comprising an enhancement molecule operably linked to said Isoleucyl-valyl-threonyl-asparaginyl-threonyl-threonine peptide, said enhancement molecule enhancing the therapeutic effectiveness of said peptide.